Topical Agents Used in the Management of Hyperpigmentation

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Disorders of hyperpigmentation are difficult to treat, particularly in dark-skinned individuals. The goal is to reduce the hyperpigmentation without causing undesirable hypopigmentation or irritation in the surrounding normally pigmented skin. The psychosocial impact caused by these disorders must be considered. Although there are many effective therapeutic modalities available, there are potentially significant side-effects associated with treatment. The most commonly used treatment is topical hydroquinone. There are other phenolic agents, such as N-acetyl-4-cystaminylphenol (NCAP), that are currently being studied and developed. The non-phenolic agents, which include tretinoin, adapalene, topical corticosteroids, azelaic acid, arbutin, kojic acid, and licorice extract, are also used for hyperpigmentation disorders.

Hyperpigmentation is a common and distressing problem caused by various inflammatory skin disorders, such as eczema, allergic contact dermatitis, and irritant contact dermatitis Acne is also a frequent cause. Papulosquamous disorders in general commonly predispose a patient to postinflammatory hyperpigmentation. Melasma is a common form of non-inflammatory hyperpigmentation.

Sun exposure often reverses the results of therapy, compromising the lengthy treatment process. Consequently, the first line of therapy for hyperpigmentation is a broad-spectrum sunscreen used in conjunction with a phenolic agent such as a hydroquinone, or with a non-phenolic agent such as tretinoin, azelaic acid, or kojic acid. There are hundreds of sunscreen formulations with different UV absorbing chemicals in various concentrations.[1] The UVB and UVA absorbing chemicals used in the formulation of topical sunscreens include para-aminobenzoic acid-related products, salicylates, cinnamates, benzophenones, zinc oxide, and titanium oxide. Almost all sunscreen products contain a mixture of one or more UVB absorbing chemicals.[1]

Hydroquinone and related compounds reduce the production of melanin by their inhibition of the enzyme tyrosinase. Topical corticosteroids also inhibit tyrosinase activity and affect endoplasmic reticulum secretory function of melanocytes. Agents such as salicylic acid and glycolic acid act to remove melanin in the epidermis by their peeling action. Tretinoin, which has a mild peeling effect, acts in a similar manner. It may also inhibit tyrosinase.

Hydroquinone, which is a hydroxyphenolic chemical, has been the gold standard for treatment of hyperpigmentation for over 50 years. It acts by inhibiting the enzyme tyrosinase, thereby reducing the conversion of DOPA to melanin. Some of the other possible mechanisms of action are the destruction of melanocytes, degradation of melanosomes, and the inhibition of the synthesis of DNA and RNA.[2]

Hydroquinone can be compounded into 5%-10% concentrations, but at these strengths, may be irritating and unstable. The 2% concentrations of hydroquinone available over the counter in the US and Canada are not as efficacious as the 3% and 4% prescription formulations, as their onset of action is later than with the higher concentrations. Antioxidants, such as vitamin C and retinoids, as well as alpha-hydroxy acids may be used as additives to increase penetration and enhance efficacy. Exogenous ochronosis with the use of hydroquinone has been reported in dark-skinned patients, in particular South African women who frequently use very high concentrations of hydroquinone over large surface areas.[3] Although hydroquinone is used extensively in North America, there have only been about 30 reported cases of exogenous ochronosis from hydroquinone use in North America.

Adverse reactions from hydroquinone use include irritant and allergic contact dermatitis, and nail discoloration. Postinflammatory hyperpigmentation may occur from the contact dermatitis. Hypopigmentation of the normal skin surrounding the treated areas may also occur. These usually resolve with the discontinuation of the hydroquinone treatment.[2]

Monobenzone, the monobenzyl ether of hydroquinone, is a special topical phenolic agent, which is indicated only for the final depigmentation of disfiguring vitiligo. It is applied topically to permanently depigment normal skin surrounding vitiliginous areas in patients with disseminated vitiligo (greater than 50% body surface area). The cream is applied in a thin layer, rubbed into the normally pigmented areas two or three times daily. Depigmentation is usually achieved after 6-12 months with 20% monobenzone treatment. It should then be applied only as often as required to maintain depigmentation. Monobenzone cream can produce satellite depigmentation at sites distant from the site of initial application.

N-acetyl-4-cysteaminylphenol (NCAP) is another phenolic agent that is currently being developed and is not yet available in North America. NCAP acts to decrease intracellular glutathione by stimulating pheomelanin rather than eumelanin.[4] It also inhibits tyrosinase activity, has been found to be more stable, and causes less irritation than hydroquinone. In a retrospective study of 12 patients with melasma using 4% NCAP, 66% showed marked improvement, and 8% showed complete loss of melasma lesions. Changes of melanoderma were evident after 2-4 weeks of daily topical application of NCAP.[5]

Azelaic acid is a naturally occurring non-phenolic, saturated, nine-carbon dicarboxylic acid. Its use originated from the finding that *Pityrosporum* species can oxidize unsaturated fatty acids to dicarboxylic acids, which competitively inhibit tyrosinase. Azelaic acid was initially developed as a topical drug with therapeutic effects for the treatment of acne. However, because of its effect on tyrosinase, it has also been used to treat melasma, lentigo maligna and other disorders of hyperpigmention.[2,6] Azelaic acid has been reported to be effective for hypermelanosis caused by physical or photochemical agents, and lentigo maligna melanoma as well as other disorders characterized by abnormal proliferation of melanocytes. Its mechanism of action is to inhibit DNA synthesis and mitochondrial enzymes, thereby inducing direct cytotoxic effects toward the melanocyte.[6] Topical azelaic acid has no depigmentation effect on normally pigmented skin, freckles, senile lentigines, and nevi. This specificity may be attributed to its selective effects on abnormal melanocytes.

Azelaic acid can be used for postinflammatory hyperpigmentation in acne.[7] Free radicals are believed to contribute to hyperpigmentation, and azelaic acid acts by reducing free radical production.[8] Azelaic acid 20% is currently available in the US and is only indicated for the treatment of acne, although it has off-label use for hyperpigmentation. In the treatment of melasma, a 24-week study in South America found that a 20% concentration of azelaic acid was equivalent to 2% hydroquinone.[9] In the Philippines, a study found that 20% azelaic acid was better than 2% hydroquinone.[10]

Kojic acid (5-hydroxy-2-(hydroxy methyl)-4-pyrone), a naturally occurring hydrophilic fungal derivative evolved from certain species of *Acetobacter*, *Aspergillus* and *Penicillium*, is used in the treatment of hyperpigmentation disorders.[11] It acts by inhibiting the production of free tyrosinase with efficacy similar to hydroquinone. In Japan, kojic acid has been increasingly used in skin care products. This is because, until recently, topically applied kojic acid at 1% concentration had not exhibited any sensitizing activity.[12] However, more recent long-term Japanese studies have shown that kojic acid has the potential for causing contact dermatitis and erythema.[12]

Arbutin, which is the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound that has been used for postinflammatory hyperpigmentation.[13] It is effective in the treatment of disorders of hyperpigmentation characterized by hyperactive melanocytes.[13] The action of arbutin is dependent on its concentration. Higher concentrations are more efficacious than lower concentrations, but they may also result in a paradoxical hyperpigmentation.[13] In comparative *in vitro* studies of various compounds used to improve the appearance of disorders of hyperpigmentation, arbutin was found to be less toxic than hydroquinone. A dose-dependent reduction in tyrosinase activity, as well as melanin content in melanocytes, was also demonstrated.[14]

Licorice extract is not yet available in North America, but has been used in other parts of the world, particularly in Egypt. Its mechanism of action is similar to that of kojic acid. The main component of the hydrophobic fraction of licorice extract is glabridin, which has an effect on the skin. Studies investigating the inhibitory effects of glabridin on melanogenesis and inflammation have shown that it inhibits tyrosinase activity of melanocytes. No effect on DNA

synthesis was detectable.[15]

The efficacy of topical tretinoin 0.05-0.1% as monotherapy for postinflammatory hyperpigmentation has been reported.[16] Tretinoin was also used as monotherapy in a study on 38 African-American patients with melasma and 68%-73% of patients improved. In 88% of the patients, moderate side-effects of desquamation and erythema were observed.[17,18] Darker skinned patients who develop a dermatitis from tretinoin may develop postinflammatory hyperpigmentation secondary to the dermatitis.

The mechanism of action of tretinoin in the treatment of melasma is poorly understood. Clinical improvement has been found to be associated with a reduction in epidermal melanin, possibly as a result of the inhibition of tyrosinase by the action of tretinoin.[19]

Although tretinoin can be effective as monotherapy for hyperpigmentation and melasma, it requires 20 to 40-week treatment periods. Tretinoin can also be used in conjunction with hydroquinone or other depigmenting agents to improve efficacy. The first published study of combination therapy used tretinoin 0.1%, hydroquinone 5%, and dexamethasone 0.1% for postinflammatory hyperpigmentation.[20] Tretinoin was shown to reduce the atrophy of the corticosteroid and facilitated the epidermal penetration of the hydroquinone. The tretinoin-induced irritation was reduced by the corticosteroid. The first triple combination topical therapy approved by the US FDA for melasma is a modified formulation comprising fluocinolone acetonide, hydroquinone 4% and tretinoin 0.05%. In studies of patients with melasma, 78% had complete or near clearing after 8 weeks of therapy. Similar results and favorable safety profile were seen in a 12-month study.[21]

In a randomized clinical trial, the efficacy of adapalene 0.1% was found to be comparable to that of tretrinoin 0.05% cream in the treatment of melasma (mainly epidermal type). The results showed fewer side-effects and greater acceptability among patients using adapalene.[19]

The treatment of hyperpigmentation disorders can be a long process. The psychosocial impact of these disorders should be taken into consideration. There are several topical treatment options available, the most common of which is hydroquinone. The use of combination therapy and monotherapy with non-phenolic agents is increasingly common. These treatment options are primarily for epidermal disorders of hyperpigmentation. Dermal disorders of hyperpigmentation are difficult to treat, and have not been effectively managed using currently available therapy.

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